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Case Report

Cystic partially differentiated nephroblastoma-like lesion following neo-adjuvant chemotherapy for nephroblastoma: A case report and review of the literature

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ABSTRACT

Cystic partially differentiated nephroblastoma (CPDN) and cystic nephroblastoma are paediatric renal tumours characterised by the presence of a variable combination of primitive epithelium, immature stroma and blastema. Cystic nephroblastoma can be identified by the presence of solid expansile areas of tumour which are absent in CPDN. The distinction can pose diagnostic difficulty pre-operatively and is of paramount importance as their metastatic potential, prognosis and hence therapeutic strategies differ.

We present a 2 year old girl, with two right renal masses, diagnosed pre-operatively as synchronous nephroblastoma based on clinical, radiological and cytologic findings. Neo-adjuvant chemotherapy was administered followed by nephrectomy. Two discrete tumours were present, one being an epithelial predominant nephroblastoma and the other a CPDN. The CPDN showed an unusual spectrum of epithelial cells lining the cysts including intestinal type epithelium with goblet cells.

This case represents one of three cases described thus far in the literature of concomitant nephroblastoma and CPDN or cystic nephroma (CN) and is the only case in which nephroblastoma occurred synchronously with CPDN. Due to neo-adjuvant therapy being instituted for the nephroblastoma, this case provides unique insights into possible chemotherapy induced changes in a CPDN (usually treated by surgical excision alone).

This case highlights several important issues in paediatric cystic renal neoplasms, particularly the distinction between cystic nephroma, CPDN and cystic nephroblastoma. The differential diagnosis of cystic paediatric renal neoplasms is broad and requires appropriate clinical, radiological and histological assessment, often with ancillary immunohistochemical and molecular studies to arrive at a correct diagnosis. Histologic features of chemotherapy effect, although well-described in nephroblastoma, are not well-described in CPDN. Based on our knowledge of possible chemotherapy induced changes in nephroblastoma, such as maturation of epithelial and stromal elements that may be so marked as to mimic mature teratoma, we hypothesize that this case demonstrates such changes within a CPDN.

1. Introduction

1.1. Case report

A two year old girl, previously well, presented with an abdominal mass which was felt by her mother two days prior to presentation. There was one episode of vomiting and stool had not been passed in two days. The mother reported that the child had lost weight, but could not quantify the period or the amount of weight loss. On examination, the child did not appear acutely or chronically unwell. Hypertension and a resting tachycardia were noted. Moderate pallor was present, as well as non-pathological cervical and inguinal lymph nodes. No dysmorphic features were present. The anthropometry and clinical nutritional state were normal. There was obvious flank asymmetry with a large, hard and ballotable right upper quadrant mass palpable. No other abnormalities were found.

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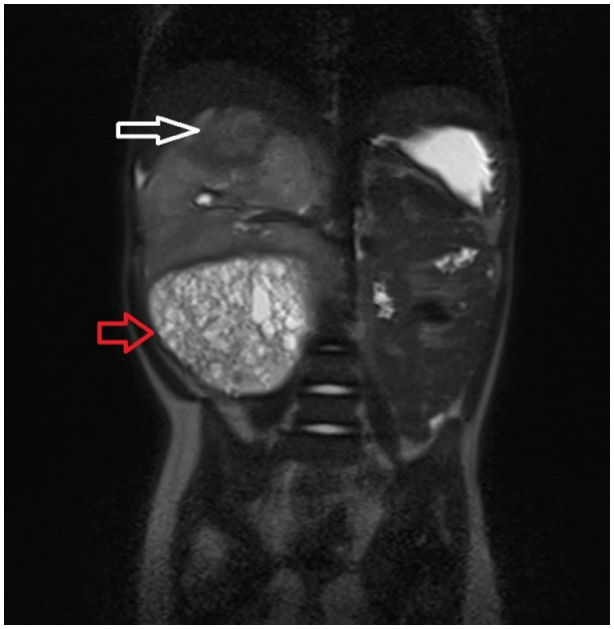

Fig. 1. MRI of the abdomen showing two lesions in the right kidney: a solid upper pole mass (white arrow) and a multicystic lower pole lesion (red arrow). (For interpretation of the references to colors in this figure legend, the reader is referred to the web version of this paper.)

An ultrasound of the abdomen revealed two masses in the right kidney. A well-defined round mass was seen in the right upper pole of the kidney (4.7 cm in diameter). A large hyperechoic mass with a claw sign was seen in the lower pole (7.2 × 5.5 × 6.4 cm).

An ultrasound-guided fine needle aspiration biopsy was performed of the upper pole mass and a cytological diagnosis of nephroblastoma was issued. The aspirate consisted predominantly of blastemal elements with a few tubular structures and some stromal tissue fragments. The lower pole mass was not aspirated. An MRI could only be obtained following the fine needle biopsy and confirmed a heterogenous right-sided upper pole mass with a well-defined capsule and a claw sign (Fig. 1). The lower pole mass was well-defined and multi-cystic, with internal septa and a fibrous capsule. No calcifications were seen. Associated hydronephrosis and hypertrophy of the right kidney, and an enlarged right renal artery were noted. There was no infiltration into the right renal vein. In addition, another well-defined peripheral nodule with associated restriction was seen adjacent to the lower pole mass in the right kidney. This was consistent with a perilobar nephrogenic rest. The left kidney was normal in size, but contained a small hyperintense focus within the lower pole, suspicious for a nephrogenic rest.

These MRI findings were suspicious for synchronous nephroblastoma in the right kidney, with right-sided nephrogenic rest and renal hypertrophy, as well as a suspicious lesion in the left kidney. No pulmonary lesions were seen on a CT scan of the chest. Based on these findings of two synchronous renal masses, one of which was confirmed on cytology to be a nephroblastoma, with a background of lesions suspicious for nephrogenic rests, the final interpretation of this case was that of synchronous nephroblastoma's with background nephroblastomatosis. Neo-adjuvant chemotherapy was thus instituted for nephroblastoma (vincristine and actinomycin weekly for 4 weeks).

Following completion of the pre-operative chemotherapy, an ultrasound of the abdomen showed enlargement of the upper pole mass in the right kidney (6 cm), as well as the lower pole mass (7.5 × 7.5 × 9.4 cm). Hydronephrosis was still seen. An uncomplicated right nephrectomy and excision biopsy of the left renal mass were performed and the child made a full recovery from surgery.

Macroscopically, two discrete, well circumscribed masses were present on coronal sectioning of the right nephrectomy specimen (Fig. 2); one in the upper pole and one in the lower pole. These masses were sharply demarcated from the adjacent renal parenchyma and had no points of communication with one another. The smaller upper pole lesion, which was sampled prior to neo-adjuvant therapy, measured 55 × 48 × 15 mm, was solid, uniform and pale grey to tan with no haemorrhage, necrosis or cyst formation. The larger lower pole lesion was entirely multicystic with no solid expansile areas and measured 115 × 130 × 130 mm.

Fig. 2. Macroscopy of the right nephrectomy specimen showing two tumours: a solid upper pole lesion and a completely multicystic lower pole lesion.

Microscopic analysis of the upper pole tumour confirmed the presence of an epithelial predominant nephroblastoma with chemotherapy effect (SIOP classification) [1]. The features included immature glomerular structures, primitive tubules and papillary structures surrounded by a compressed fibrous pseudocapsule (Fig. 3). Residual primitive stroma and blastema were absent, and no foci of anaplasia were demonstrated. The features interpreted as chemotherapy effect were a fibro-myxomatous stroma containing lipid- and hemosiderin-laden macrophages as well as absence of the blastemal elements seen on pre-therapy cytology (Fig. 4).

The lower pole tumour comprised multiple large cysts separated by loose stroma with no solid or expansile foci despite extensive sampling. Occasional compressed glomeruloid structures were present. The

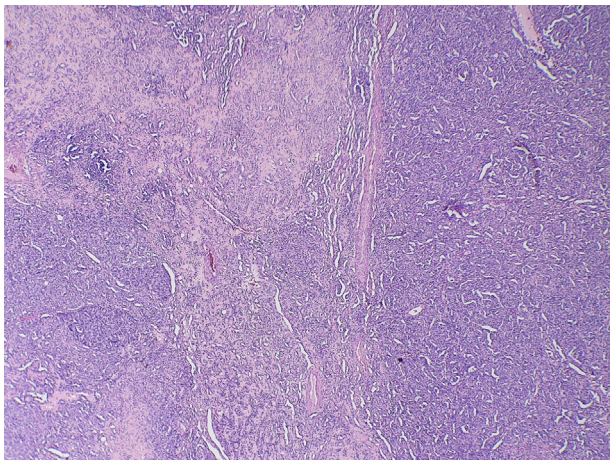

Fig. 3. H&E 40x Epithelial predominant nephroblastoma (Upper pole tumour).

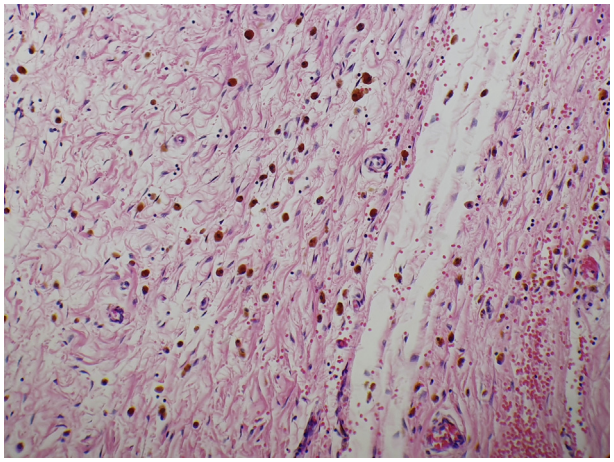

Fig. 4. H&E 400x Chemotherapy induced changes in the nephroblastoma – fibromyxoid stroma, hemosiderin laden macrophages and haemorrhage.

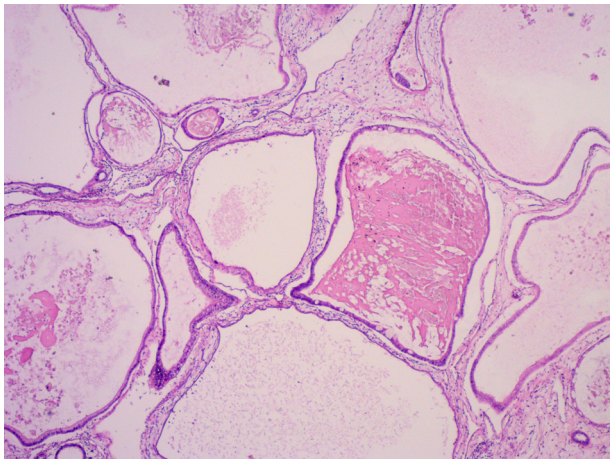

Fig. 5. H&E 40x lower pole lesion showing multiple cysts lined by a spectrum of epithelial types including attenuated cuboidal, columnar and mucinous with goblet cells.

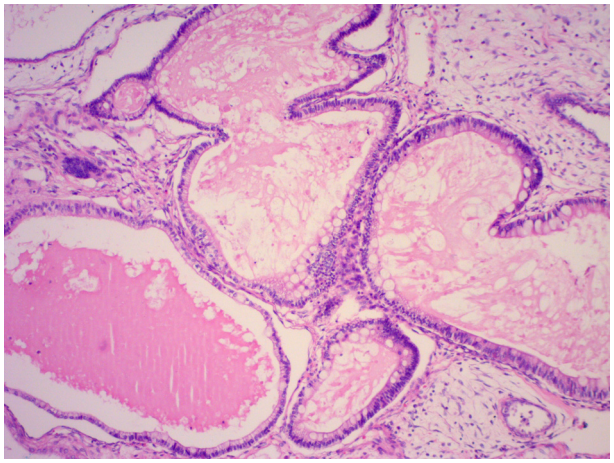

Fig. 6. H&E 100x lower pole lesion showing multiple cysts lined by a spectrum of epithelial types including attenuated cuboidal and columnar.

intervening stroma appeared primitive and oedematous, featuring a mild chronic inflammatory cell infiltrate. Blastema and mature stromal elements were absent. The cysts were lined by a spectrum of epithelia including attenuated cuboidal, low columnar, tall stratified columnar, hobnailing, and intestinal mucinous epithelium with goblet cells

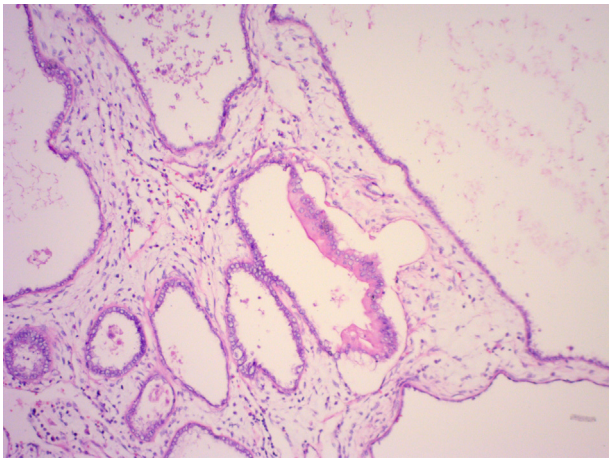

Fig. 7. H&E 100x lower pole lesion showing multiple cysts lined by a spectrum of epithelial types including columnar and mucinous with goblet cells.

(Figs. 5–7).

The epithelial lining of the cysts in the lower pole lesion was positive for pancytokeratin (MNF-116), with focal positive staining for cytokeratin 7 and 20, CDX2, P504S (Racemase), SALL4 and EMA. Vimentin, CD56 and Glypican-3 were negative in the epithelium. The compressed glomeruloid structures between cysts were positive for WT1.

Hyperplastic perilobar nephrogenic rests were present in the background kidney, in keeping with the pre-operative MRI findings. The lesion seen on MRI of the left kidney was a scar with renal cysts.

A final diagnosis of an upper pole epithelial predominant nephroblastoma with chemotherapy effect and background hyperplastic perilobar nephrogenic rests was made. The lower pole mass was diagnosed as a cystic partially differentiated nephroblastoma-like lesion with a comment on the possible differential diagnoses (see discussion below). The child received another 4 weeks of post-operative chemotherapy (vincristine and actinomycin D) and is currently well, attending a long-term follow-up clinic.

2. Discussion

We present an interesting case of a nephroblastoma with a synchronous CPDN-like lesion and a background of hyperplastic nephrogenic rests that was treated with neo-adjuvant chemotherapy. The nephroblastoma was confirmed on pre-therapy cytology and at nephrectomy showed an epithelial predominant nephroblastoma with chemotherapy effect. The cystic lesion did not have pre-therapy cytology/histology. Based on the imaging findings and the occurrence with a confirmed nephroblastoma and suspected nephrogenic rests, this cystic lesion was interpreted pre-operatively as most likely to be a synchronous cystic nephroblastoma. Histology of this lesion however showed only features of a CPDN with no solid expansile areas despite extensive sampling. Interestingly this lesion also showed unusual epithelial cells lining the cysts including intestinal type epithelium with goblet cells. This case highlights several important issues in this setting including the differential diagnosis of paediatric cystic renal neoplasms, features that can be useful to distinguish these lesions from one another, the histologic features seen in response to chemotherapy and the possible concomitant occurrence of more than one of these lesions. These issues are discussed below.

The differential diagnosis of multicystic paediatric renal masses is broad and includes cystic nephroma (CN), cystic partially differentiated nephroblastoma (CPDN), cystic nephroblastoma, cystic renal cell carcinoma, cystic congenital mesoblastic nephroma, localised cystic kidney disease and although rarely cystic, clear cell sarcoma and renal rhabdoid tumour. CN and CPDN are however the only two primary

paediatric cystic renal neoplasms that are exclusively cystic and should therefore be strongly considered in cases with no solid areas [1]. Several features that are unique to nephroblastoma may help to distinguish it from these other differentials. These include the presence of bilateral or multifocal disease, background nephrogenic rests, associated syndromes (Denys-Drash, WAGR, Beckwith-Weideman) and the presence of skeletal muscle, adipose tissue and neoplastic tubules. Patient age, morphology and immunohistochemistry (such as INI1 in renal rhabdoid tumour [2], BCOR in clear cell sarcoma [3], pan-TRK in mesoblastic nephroma [4]), may help resolve the other differential considerations.

Cystic partially differentiated nephroblastoma was first described by Brown in 1975 [5]. It represents a well demarcated discrete mass composed entirely of cysts with an absence of solid areas [1,5]. The cyst walls are lined by flattened to hobnailed epithelium with a variable component of blastema, immature epithelium or immature stroma within thin fibrous septa [1,5]. It occurs more commonly in males under two years of age [6]. It is distinguished from CN by the presence of embryonal cell types (blastema, immature epithelium or immature stroma) within the septa [7]. CN and CPDN are both treated by surgical excision alone and share an excellent prognosis [6,8].

Cystic nephroblastoma is distinguished from the former two entities by the presence of a solid expansile mass(es) which distort the contours of the cyst(s) and may comprise an admixture of blastema, immature epithelium and primitive stroma, although one or more of these may predominate [6]. Nephroblastoma is treated with surgery, chemotherapy and radiotherapy (either pre-operatively or post-operatively). The sequence of treatment modalities depends on the protocol being followed (i.e. SIOP vs. COG protocols) [1]. CN and CPDN are treated with surgical resection alone requiring no adjuvant chemotherapy and the distinction of these lesions from nephroblastoma is therefore of paramount importance [9].

In the past CN, CPDN and cystic nephroblastoma were considered to be related tumours on a spectrum of differentiation [10]. Recent studies into the biological profile of these tumours have however shown that CN and CPDN are not related entities and importantly paediatric CN is associated with DICER1 mutations [11]. It has been proposed, but never proven, that nephroblastoma may undergo maturation to a CPDN analogous to maturation of a neuroblastoma to a ganglioneuroma [12,13]. The diagnostic challenges posed by these three neoplasms preoperatively and histologically is well known and has been the subject of many articles [14,15].

Concomitant CN/CPDN and Wilms Tumour have been described [16,17]. In one of these cases, a 9 month old infant presented with bilateral cystic masses radiologically in keeping with CPDN [16]. Bilateral partial nephrectomies were undertaken with histologic conformation of CPDN. Six months follow-up revealed recurrence of the masses which were again excised. The histology of the recurrence was that of cystic nephroblastoma. The second case occurred in a 21 month old girl and presented as synchronous tumours separated by a fibrous capsule [17]. Histology of the lesions was that of a triphasic nephroblastoma and a CN. Our case is similar to the second case described here in that the neoplasms were synchronous and both occurred in slightly older children (21 and 24 months). Our case did however show embryonal cells within the fibrous septae in keeping with CPDN.

Chemotherapy-induced changes are well described in nephroblastoma and include necrosis of predominately mitotically active blastemal components with potentially massive necrosis and shrinkage of the tumour [18]. Maturation and differentiation of epithelial and stromal components is also described and may mimic teratoma with endodermal, ectodermal and mesenchymal differentiation [19,20]. Chemotherapeutic changes in CPDN and CN are not described in the literature, as surgical excision is the treatment of choice. One of the cases described above of a synchronous nephroblastoma and CN received pre-operative neo-adjuvant chemotherapy. No treatment related changes were described in the CN component although necrosis was seen in the nephroblastoma [17].

There are two possible interpretations of the histologic findings in our case. One, which we favour, is that of a nephroblastoma and a concurrent CPDN. The other interpretation is that of synchronous nephroblastoma's, one of which was cystic, with extensive chemotherapy-induced changes leaving no solid expansile areas behind. The pre-therapy imaging of an exclusively multicystic lesion would favour the first interpretation. Extensive chemotherapy induced changes in a nephroblastoma resulting in morphology of a CPDN has not been described in the literature. We hypothesize that the spectrum of epithelial types seen in the CPDN, including intestinal epithelium with goblet cells, represents chemotherapy induced changes as has been described in nephroblastoma, but not to our knowledge previously in CPDN.

3. Conclusion

CPDN and nephroblastoma are paediatric renal neoplasms that demonstrate a variable combination of primitive epithelium, immature stroma and blastema, and differ in the lack of solid expansile areas in the former. The distinction is important as prognosis, rate of recurrence and therapeutic strategies differ, with nephroblastoma potentially requiring addition of chemotherapy and/or radiotherapy to surgical excision. Previous publications have highlighted the diagnostic difficulty in distinguishing between CPDN and cystic nephroblastoma pre-operatively [14]. The histologic distinction is made more difficult by the addition of chemotherapy-induced changes in these lesions. We report an unusual case of a CPDN with a concomitant nephroblastoma. We hypothesize that the unusual finding of extensive intestinal type epithelium lining cysts of the CPDN represents chemotherapy induced changes in a CPDN that have not been previously described.

Patient consent statement

Written informed consent was obtained from the patient for publication of this case report.

Declaration of Competing Interest

The authors declare that they have no conflict of interest. No funding was received for this work.

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